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DOI: https://doi.org/10.1093/clinids/4.supplement_3.s581

REVIEWS OF INFECTIOUS DISEASES • VOL. 4, SUPPLEMENT • NOVEMBER-DECEMBER 1982
 0162-0886/82/0406-0017$02.00

Comparative Multiple-Dose Pharmacokinetics of Cefotaxime, Moxalactam, and Ceftazidime

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The present study was conducted to compare the pharmacokinetics of three different doses of cefotaxime, moxalactam, and ceftazidime and to evaluate the influence of probenecid on the pharmacokinetic behavior of these three third-generation cephalosporins.

Patients and Methods

Six male volunteers received in a crossover fashion doses of 0.5, 1.0, and 2.0 g of each drug by infusion over a 5-min interval. Doses of 1.0 g were repeated after administration of probenecid. For each dose, 17 blood samples per volunteer were drawn for documentation of the distribution and elimination phase of the cephalosporin. The urinary excretion was determined from five quantitative urine collections made over the 24-hr period after administration of the test drug. Serum and urine concentrations were assayed by an agar diffusion method. The assay strain for cefotaxime was resistant to its desacetyl metabolite. The average coefficient of variation for interassay precision was 4.6% ± 0.9%. Serum samples for the 0.5- and 2.0-g doses of cefotaxime and moxalactam also were analyzed by a method of high-pressure liquid chromatography (HPLC) that provided information on the behavior of the desacetyl metabolite of cefotaxime and the two naturally occurring epimers of moxalactam [1, 2]. The pharmacokinetic parameters of a two-compartment open model were adapted to the experimental data with a nonlinear fitting program. For all statistical evaluations the Wilcoxon matched pairs signed rank test was used. Probabilities of $2\alpha \leq 0.05$ were considered significant.

Results and Discussion

The mean serum concentrations of cefotaxime, moxalactam, and ceftazidime at 10 min and 6, 8, and 12 hr are presented in table 1. Serum concentrations of moxalactam exceeded those of ceftazidime at all times and were distinctly higher than those of cefotaxime. At 8 and 12 hr the mean concentrations of cefotaxime were consistently <0.5 mg/liter, whereas those of ceftazidime and moxalactam were ~5–10 times higher. For facilitation of the comparison between the various doses and drugs, the area under the serum concentration-vs.-time curve (AUC) was normalized by dividing by the individual dose. Compared with the value for cefotaxime, the normalized AUC for moxalactam was three to four times higher and that for ceftazidime, two to three times higher. Probenecid increased the AUC for the 1.0-g dose of cefotaxime about twofold but did not affect those for moxalactam and ceftazidime significantly. Linear regression analysis of the dose (x [in g]) vs. normalized AUC (y [in mg × hr/liter]) yielded a slope for cefotaxime ($y = 13.14x + 45.12$) that was significantly different from zero ($P < 0.001$), a result that indicated a nonlinear increment in AUC for increasing doses. In contrast, slopes for moxalactam ($y = -19.36x + 240.09$) and ceftazidime ($y = -14.59x + 168.51$) did not differ significantly from zero.

The pharmacokinetic parameters of cefotaxime, moxalactam, and ceftazidime are summarized in table 2. Significant differences between the three compounds in the total volume of distribution were observed for the 0.5-g dose but not for the 1.0- and 2.0-g doses. Intraindividual comparisons of the elimination t½ values, total body clearance rate, and renal clearance rate demonstrated

This paper is an extended abstract of a paper published in *Antimicrobial Agents and Chemotherapy* 20:567–575, 1981.

Informed consent according to institutional policies was obtained from each study participant.

This study was supported in part by grants from Lilly Research Laboratories and Glaxo Group Research, Ltd.

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Table 1. Mean serum concentrations of drug after infusions over a 5-min interval of cefotaxime, moxalactam, and ceftazidime in six male volunteers.

Dose, drug	Actual dose (g)*	Mean ± SD serum level (mg/liter)			
		0.17 hr	6 hr	8 hr	12 hr
0.5 g					
Cefotaxime	0.58	37.8 ± 7.1	0.3†	<0.1	<0.1
Moxalactam	0.47	63.3 ± 6.0	4.2 ± 1.7	2.2 ± 0.6	0.7 ± 0.2
Ceftazidime	0.48	49.9 ± 8.0	2.1 ± 0.5	1.0 ± 0.3	0.3 ± 0.1
1 g					
Cefotaxime	1.06	80.8 ± 14.1	0.4 ± 0.1	<0.1	<0.1
Moxalactam	0.99	120 ± 12.4	8.2 ± 2.0	4.7 ± 1.0	1.4 ± 0.5
Ceftazidime	0.96	107 ± 18.0	4.4 ± 1.4	2.1 ± 0.7	0.5 ± 0.3
2 g					
Cefotaxime	2.02	174 ± 36.7	0.9 ± 0.5	0.5‡	<0.1
Moxalactam	1.87	210 ± 30.8	14.2 ± 2.4	8.0 ± 1.8	2.6 ± 0.8
Ceftazidime	1.94	181 ± 23.2	6.6 ± 1.5	3.8 ± 0.9	1.1 ± 0.5
1 g + probenecid§					
Cefotaxime	0.96	109 ± 12.3	1.4 ± 0.7	0.6‖	<0.1
Moxalactam	1.10	111 ± 10.8	10.0 ± 1.7	6.2 ± 1.2	2.7 ± 0.8
Ceftazidime	0.97	98.9 ± 12.5	4.2 ± 0.6	2.1 ± 0.5	0.5 ± 0.2

* Mean value of the doses administered to the six volunteers.

† The SD for three volunteers was 0.1; that for the other three was <0.1.

‡ The SD for three volunteers was 0.4; that for the other three was <0.1.

§ Probenecid was administered at a dosage of 0.5 g every 6 hr on the day before testing and 1.0 g at 30 min before administration of the test drug.

‖ The SD for five volunteers was 0.4; that for the remaining volunteer was <0.1.

significant differences between these antibiotics. The t½ values, calculated from the 0.5-, 1.0-, and 2.0-g doses, averaged 2.34, 1.95, and 1.16 hr for moxalactam, ceftazidime, and cefotaxime, respectively. The 24-hr urinary recovery was highest for moxalactam (75% ± 4%), followed by ceftazidime (68% ± 11%) and cefotaxime (53% ± 6%). The total body and renal clearance rates of cefotaxime decreased significantly with an increase in the dose. In contrast to the findings for moxalactam and ceftazidime, the ratio of renal clearance rate to creatinine clearance rate for cefotaxime indicated considerable tubular secretion of the drug.

The influence of probenecid on serum concentration, t½, AUC, volume of distribution, and clearance rate was most obvious with cefotaxime. Saturation of tubular secretion led to serum concentrations with the 1.0-g dose of cefotaxime that at 2 hr already were higher than those achieved with the 2.0-g dose. The renal clearance rate of this drug decreased by almost 50% and the AUC doubled when probenecid was administered. This finding is in contrast to the findings for moxalactam and ceftazidime, where the marginal influence of this agent is of no practical significance.

The level of the desacetyl metabolite of cefotaxime, determined by HPLC, peaked 45 min after administration. The average levels of the metabolite were 2.7 ± 1.0 and 9.8 ± 1.8 mg/liter for the 0.5- and 2.0-g dose, respectively, and the half lives for these doses were approximately twice those of cefotaxime (1.9 ± 0.7 hr and 1.4 ± 0.4 hr, respectively). After the 0.5-g dose the AUC for the desacetyl metabolite was 31% ± 12% of the AUC for cefotaxime. For the 2.0-g dose this proportion decreased to 18% ± 2%, a result suggesting that desacetylation may not follow first-order kinetics.

Freshly prepared solutions of moxalactam contain two epimers, designated R(−) and S(−), in approximately equal amounts. The serum protein binding of the R(−) epimer averages 53%; that of the S(−) epimer is ~67% [3]. The antimicrobial activity of the former epimer is approximately double that of S(−) [1].

Analysis of the two epimers revealed that their pharmacokinetic behaviors are different. At 10 min after iv administration, the ratio of the R(−) to the S(−) epimer was 0.84; it decreased rapidly to 0.5 at 5 hr—i.e., there was twice as much of the S(−) epimer as of the R(−) epimer. At this time

Table 2. Summary of the pharmacokinetic parameters of cefotaxime, moxalactam, and ceftazidime.

Drug, dose (g)	V_1 (liter/kg)	V_D (liter/kg)	k_{12} ($\times 10^{-4}$/hr)	k_{21} ($\times 10^{-4}$/hr)	t½ (hr)	Cl_B (ml/min)	Urinary excretion (%)	Cl_R (ml/min)	Cl_{Cr} (ml/min)	Ratio Cl_R/Cl_{Cr}
Cefotaxime										
0.5	0.17 ± 0.04	0.29 ± 0.05	2.30 ± 1.10	3.05 ± 1.12	1.10 ± 0.38	391 ± 97	58 ± 12	217 ± 31	129 ± 18	1.69 ± 0.11
1.0	0.14 ± 0.03	0.24 ± 0.04	2.10 ± 0.72	2.98 ± 0.85	1.08 ± 0.27	326 ± 48	47 ± 7.9	154 ± 38	132 ± 16	1.16 ± 0.22
2.0	0.15 ± 0.02	0.21 ± 0.04	1.00 ± 0.43	2.13 ± 0.73	1.31 ± 0.32	267 ± 49	56 ± 18	145 ± 48	141 ± 18	1.03 ± 0.29
1.0 + probenecid*	0.10 ± 0.01	0.18 ± 0.02	3.40 ± 0.82	3.97 ± 0.55	1.15 ± 0.03	169 ± 16	51 ± 3.6	85 ± 8.8	124 ± 10	0.69 ± 0.10
Moxalactam										
0.5	0.09 ± 0.01	0.18 ± 0.01	2.45 ± 0.60	2.63 ± 0.73	2.35 ± 0.32	77.8 ± 9.4	79 ± 4.8	61.7 ± 9.0	135 ± 18	0.46 ± 0.06
1.0	0.10 ± 0.01	0.19 ± 0.01	3.35 ± 1.18	3.47 ± 1.03	2.25 ± 0.21	81.2 ± 10.6	71 ± 7.3	58.0 ± 9.2	140 ± 17	0.41 ± 0.05
2.0	0.12 ± 0.02	0.23 ± 0.03	2.33 ± 0.97	2.48 ± 0.47	2.42 ± 0.13	94.4 ± 15.7	73 ± 5.2	69.4 ± 14.6	141 ± 10	0.49 ± 0.08
1.0 + probenecid*	0.13 ± 0.02	0.24 ± 0.02	2.38 ± 0.67	2.53 ± 0.47	2.79 ± 0.24	83.2 ± 9.6	67 ± 6.9	55.7 ± 11.6	130 ± 16	0.43 ± 0.10
Ceftazidime										
0.5	0.14 ± 0.01	0.22 ± 0.02	1.05 ± 0.18	1.97 ± 0.33	2.01 ± 0.16	144 ± 16	66 ± 2.8	75.1 ± 11.6	131 ± 24	0.58 ± 0.09
1.0	0.13 ± 0.02	0.21 ± 0.02	1.48 ± 0.53	2.18 ± 0.33	1.87 ± 0.15	116 ± 18	75 ± 3.3	87.6 ± 16.1	143 ± 24	0.61 ± 0.05
2.0	0.14 ± 0.01	0.25 ± 0.02	1.78 ± 0.65	2.37 ± 0.65	1.96 ± 0.18	133 ± 20	60 ± 9.1	81.1 ± 17.6	121 ± 12	0.67 ± 0.12
1.0 + probenecid*	0.13 ± 0.01	0.21 ± 0.01	1.32 ± 0.20	2.23 ± 0.35	1.97 ± 0.17	114 ± 13	68 ± 4.2	78.6 ± 9.4	133 ± 44	0.64 ± 0.19

NOTE. A two-compartment model was used, and the volume of distribution of the central compartment (V_1), the total volume of distribution (V_D), the rate constants of transfer between the two compartments (k_{12} and k_{21}), the terminal t½, the total body clearance rate (Cl_B), the percentage of the administered dose excreted in urine, the renal clearance rate (Cl_R), and the creatinine clearance rate (Cl_{Cr}) were calculated. The values for cefotaxime were derived by fitting the model to the data for the first 6 hr only, whereas those for moxalactam and ceftazidime were derived by fitting the model to all of the data. The data are mean ± SD values for six male volunteers.

* Probenecid was administered at a dosage of 0.5 g every 6 hr on the day before testing and 1.0 g at 30 min before administration of the test drug.

the antimicrobial activity, as determined by the agar diffusion assay, was reduced by one-fourth when compared with the concentration measured by HPLC analysis.

No adverse effects were recorded throughout the study. Chemistry profiles, blood cell counts, urinalysis results, and creatinine clearance rates remained within normal limits.

The present study demonstrated that significant differences exist in the pharmacokinetic behavior of cefotaxime, moxalactam, and ceftazidime. From this standpoint, it appears reasonable to conclude that moxalactam and possibly ceftazidime could be administered twice a day and cefotaxime, three or even four times a day.

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